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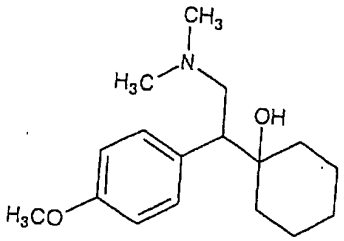
(54) Title: EXTENDED RELEASE COMPOSITIONS COMPRISING AS ACTIVE COMPOUND VENLAFAXINE HYDROCHLORIDE

(57) Abstract: The present invention relates to an extended release composition comprising as active compound Venlafaxine Hydrochloride, in which Venlafaxine Hydrochloride is coated on a non pareil inert core, which coated core is then coated with polymeric layer which enables the controlled release of the Venlafaxine Hydrochloride.

Extended Release Compositions Comprising As Active Compound Venlafaxine Hydrochloride

The present invention relates to extended release compositions comprising as active compound Venlafaxine Hydrochloride.

Venlafaxine Hydrochloride is an antidepressant having formula 1



being designated (R/S)-1- [2-(dinehylamino) – 1 – (4- methoxyphenyl) ethy1] cyclohexanol hydrochloride or (±) – 1 – [a] (dimethylamino) methyl] p-methoxybenzyl cyclohexanol hydrochloride, having the empirical formula of C17H27NO2 hydrochloride and molecular weight of 313.87.

Venlafaxine hydrochloride is a white to off white crystalline solid with a solubility of 572 mg/ml in water (adjustment to ionic strength of 0.2 M with sodium chloride). Its octanol: water (0.2 M sodium chloride) partition coefficient 0.43. Effexor XR the Brand product is formulated as an extended release capsule for once a day oral administration.

The drug release has so far been controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Known capsules containing Venlafaxine Hydrochloride comprise amounts equivalent to 37.5 mg, 75 mg, or 150 mg of Venlafaxine. The inactive ingredients are mainly cellulose, ethylcellulose, gelatin, hydroxypropyl methylcellulose, iron oxide, and titanium dioxide.

Controlled or extended release dosage forms of medicament are conventionally produced as hydrogel matrix based tablets. At this technology the controlled release dosage forms are simply prepared by mixing the active material with the appropriate rate of controlling polymers and then that mixture is compressed into the desired controlled release tablets. The rate controlling polymers are normally termed as hydrogels. Examples of such polymers are cellulose ethers such as ethyl cellulose or hydroxypropylcellulose. Patents describing preparation methods of such

dosage forms are described for example in US Patent Specifications 4,966,768 or 4,389,393.

In some cases, for example with very water soluble active materials and with relatively high doses it is not feasible to produce tablets which enable appropriate control on the drugs release. This is the case, for example with Venlafaxine Hydrochloride.

In such a case a suitable approach is encapsulating the drug and producing extended release capsules dosage forms. When preparation of such dosage forms is considered, the preferred way is to mix the active ingredient with at least one binding agent to form a uniform
mixture which is later moistended with water or with an appropriate organic solvent to form an extrudable plastic mass, from which small particles, cylinders shape (1mm diameter) of drug / matrix are extruded, chopped into appropriate lengths and converted to spheroids using spheronization equipment. These spheroids are further dried and than film coated with an appropriate polymer to form a film with the desired release patterns. The most widely used excipient in the extruding process is microcrystalline cellulose in its different grades ,usually water is used for the wetting process.

Polymers widely used for coating are ethyl cellulose or Eudragit (Ammonio methacrylate copolymer, type A or B). Water soluble ingredients are normally mixed with the ethyl cellulose or with other hydrophobic polymers, such as pore forming agents to assist the control on the drugs release through the hydrophobic coating layer. The water soluble ingredients such as hydroxypropyl cellulose or polyethylene glycol may serve as plasticizers as well.

Venlafaxine Hydrochloride has so far been formulated into a controlled release dosage form with the ability to provide in a single dose a therapeutic blood serum level of the drug over a twenty four hour period. By this method, tighter plasma therapeutic range control can be obtained and a multiple dosing is avoided in this manner. The sharp peaks and troughs in blood plasma drug levels are avoided as well.

With the conventional release dosage forms of Venlafaxine Hydrochloride (tablets), peak blood plasma levels appeared after 2-4 hrs, in contrast to the extended release dosage forms, when plasma levels of Venlafaxine Hydrochloride

rose after administration for between five to eight hrs (average – 6) and than begin to fall through a protracted, substantially linear decrease from the peak plasma level for the reminder of the period, maintaining therapeutic level of the drug during the entire twenty four hours period.

In WO 99/22724 (AHP, Sherman) a detailed description of preparating an encapsulated dosage form (coated spheroids) of Venlafaxine Hydrochloride is provided. By the method described therein, a spheroid core is prepared by extruding and spheronizing a mixture of the drug with microcrystalline cellulose, and than coating it with an ethyl cellulose hydroxypropylcellulose mixture.

This dosage form provides an extended release product with the following in vitro dissolution specifications:

Time (hrs)	Average % venlafaxine HCL release
2	<30
4	30-55
8	55-80
12	65-90
24	>80

These dissolution characteristics are pH, RPM independent.

In the present invention an alternative once daily bioequivalent formulation to the innovators one (Effexor XR, described in WO 99/22724) has been developed.

As already mentioned, with high dose water soluble product such as Venlafaxine Hydrochloride (150mg), the usual preferred way of encapsulating it is by preparing and coating an appropriate beads, using the extrusion spheronization process.

In the present invention the microencapsulation has been changed, i.e. is being performed by layering the drug over an inert pareil core, and than coating it with an appropriate polymeric mixture.

The present invention thus consists in an extended release composition comprising as active compound Venlafaxine Hydrochloride, in which Venlafaxine Hydrochloride is coated on a non pareil inert core, which coated core is then coated

with a polymeric layer which enables the controlled release of the Venlafaxine Hydrochloride.

The composition preferably comprises 30 – 60% of Venlafaxine Hydrochloride per weight of the total dosage form.

In a preferred embodiment of the present invention, the Venlafaxine Hydrochloride is suitably connected to a binder, said binder may be e.g. polyvinyl pyrrolidone (povidone), hydroxypropylcellulose, hydroxypropylmethylcellulose, etc. The composition preferably comprises 0.5% - 10% of the binder per weight of the total dosage form.

Advantageously the non pareil inert core is an inert sugar core, a microcrystalline cellulose or the like. The composition preferably comprises 30 – 60% of the core per weight of the total dosage form.

Alternatively the drug might be sprayed as it is and the water is then used as binding enhancement agent.

Advantageously the coated core is coated with an isolating/protecting/separating layer, which layer is suitably composed of polymers such as polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystallinecellulose, carrageenan, GMS etc. The composition preferably comprises 0.5 – 10% of the isolating layer per weight of the total dosage form.

The core or the isolating layer is coated then with an additional polymeric layer which enables the controlled release of Venlafaxine Hydrochloride. Said additional polymeric layer is composed, e.g. of a hydrophobic polymer mixed with an appropriate hydrophobic or hydrophilic plasticizer. Said polymeric layer is suitably sprayed over the coated non pareil layer or over the isolating layer.

Appropriate coating polymers are, e.g. Eudragit, cellulose derivatives such as hydroxypropylmethylcellulose, ethyl cellulose, cellulose acetate, etc. Their suitable plasticizers are, e.g. castor oil, dibutyl sebacate, glyceryl monostearate, diethyl phtalate, glyceryl trihepthanoate, triethyl citrate, etc.

The coating polymeric layer may also be a wax based coating.

The composition preferrably comprises 2 – 15% of the hydrophobic polymer per weight of the total dosage form; and preferably 0.1 – 2% per weight of the hydrophobic plasticizer per weight of the total dosage form.

The above processes are conventional processes that may be performed in a fluid bed coater with a bottom spraying mechanism.

In the composition according to the present invention, preferably not more than 40% of the drug are released after two hours, not more than 60% released after 4 hours and not more than 80% after 8 hours.

The compositions obtained are suitably, e.g. filled into hard gelatin capsules or compressed into tablets.

This formulation has an identical in vitro dissolution profile as Effexor XR (see Sherman, WO99/22724). They are not sensitive to any changes in dissolution conditions. It is bioequivalent to Effexor XR 150 mg caps.

The coating process being used to produce the composition according to the present invention is more efficient than the method being used at the Sherman patent. Moreover, it enables the preparation of the drug in a single type of equipment, e.g. a fluid bed coater.

The present invention will now be illustrated with reference to the following examples without being limited by them.

The process preparing the composition according to the present invention is suitably performed as follows (all temperatures are given in degrees centigrade):

a. When Venlafaxine Hydrochloride is connected to a binder the Venlafaxine Hydrochloride is connected to the binder by methods know per se.

b. Stage 1

Coating the non pareil core with the Venlafaxine Hydrochloride (advantageously connected with a binder) is performed at an inlet temperature of 45° – 55° (preferably at 50°) at an outlet temperature of 35° – 45° (preferably at 40°).

At the end of the spraying process, the composition is dried for 10 minutes without nozzle with 30 cfm air flow.

c. Stage 2

The coated core obtained in Stage 1 is coated with the insulating layer at an inlet temperature of 60° +/- 3° at an outlet temperature of 50° +/- 2.

d. Stage 3 (when an insulating layer is present in Stage 2)

The core is coated with a further preliminary layer, the conditions of said coating are:

Inlet temp: - 50° +/- 2

Outlet temp: - 40° +/- 5

Example No. 1 (without binder)

Stage 1: Components - Non pareils 25/30 150gr
Venlafaxine Hydrochloride 37.5gr
H2O 150gr.

Stage 2: Components – 150gr layered pellets from stage 1
Ethocel 45cp–15gr
Methocel 5cp–1gr
Ethanol BP 300gr

At the end of the spray process the composition for 10 minutes without nozzle with 30 cfm.

Example No. 2

Stage 1: components – Non pareils (inert sugar pellets) 150gr
Povidone K–30– 3.3gr.
Venlafaxine Hydrochloride– 165gr.
Ethanol BP– 670gr.

Stage 2: components – 150gr. layered pellets from stage 1
Ethocel 45 cp.– 15gr
Methocel 5 cp– 1gr
Ethanol BP– 300gr

The coating process was performed in a "4" fluid bed coater made by Coating Place Inc. USA.

Example No. 3:

Stage 1: components – Non pareils 25/30 – 150gr
Venlafaxine Hydrochloride 37.5gr
Povidone K–30– 0.75gr
Ethanol BP– 160gr

Stage 2: components – 150gr layered pellets from stage 1

Eudragit RS 30 D– 150gr

Triethyl citrate– 9gr

Glycerol monostearate– 2.25gr

Polysorbate 80– 1gr

Water– 140gr

The coating process was performed in a "4" fluid bed coater, made by Coating Place Inc. USA.

Example No. 4:

Stage 1: components – Non-pareils 25/30- 150gr.
Povidone K –30- 0.75 gr.
Venlafaxine HCL -37.5 gr.
Ethanol BP -160gr.

Stage 2: components – 150 gr. pellets from stage 1.
Eudragit RS 30D- 150 gr.
Eudragit RL 30D- 15 gr.
Triethyl citrate- 9 gr.
Glycerol monostearate- 2.25 gr.
Polysorbate 80-1gr
Water- 140 gr.

All processes were performed in a "4" fluid bed coater, made by Coating Place Inc. USA.

Example no.5:

Stage 1: components – 150 gr. Non pareils 25/30
Povidene K – 90 -4.5 gr.
Venlafaxine HCL- 150gr.
Ethanol BP- 670 gr.
Water-110 gr

Stage 2: components – 150 gr. Pellets from stage 1
Povidone K – 30- 3.75 gr.
Ethanol absolute -60 gr.

Stage 3: components – Pellets from stage 2
Ethocel 100 cp.- 8 gr.
Dibutyl sebacate- 0.8 gr.
Ethanol absolute -300 gr.

CLAIMS

1. An extended release composition comprising as active compound Venlafaxine Hydrochloride, in which Venlafaxine Hydrochloride is coated on a non pareil inert core, which coated core is then coated with a polymeric layer which enables the controlled release of the Venlafaxine Hydrochloride.
2. A composition according to Claim 1, wherein the composition comprises 30 – 60% of Venlafaxine Hydrochloride per weight of the total dosage form.
3. A composition according to Claim 1 or 2, wherein the Venlafaxine Hydrochloride is suitably connected to a binder.
4. A composition according to Claim 3, wherein the binder is selected among polyvinyl pyrrolidone (povidone), hydroxypropylcellulose and hydroxypropylmethylcellulose.
5. A composition according to Claim 3 or 4, wherein the composition comprises 0.5% - 10% of the binder per weight of the total dosage form.
6. A composition according to any of Claims 1 to 5, wherein the non pareil inert core is an inert sugar core, a microcrystalline cellulose or the like.
7. A composition according to any of Claims 1 to 6, which comprises 30 – 60% of the core per weight of the total dosage form.
8. A composition according to any of Claims 1 to 7, wherein the core is coated with an isolating/protecting/separating layer.
9. A composition according to Claim 8, wherein the isolating layer is composed of polymers such as polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline, cellulose, carrageenan, GMS.
10. A composition according to Claim 8 or 9, wherein the isolating layer is comprised of 0.5 – 10% of the isolating layer per weight of the total dosage form.
11. A composition according to any of Claims 1 to 10, being coated with an additional polymeric layer.

12. A composition according to Claim 11, wherein said additional polymeric layer is composed, e.g. of a hydrophobic polymer mixed with an appropriate hydrophobic or hydrophilic plasticizer.
13. A composition according to Claim 12, wherein said coating polymers are selected among Eudragit, cellulose derivatives such as hydroxypropylmethylcellulose, ethyl cellulose, cellulose acetate and their plasticizers are selected among castor oil, dibutyl sebacate, glyceryl monostearate, diethyl phtalate, glyceryl trihepthanoate, triethyl citrate.
14. A composition according to any of Claims 12 or 13, which comprises 2 – 15% of the hydrophobic polymer per weight of the total dosage form; and 0.1 – 2% per weight of the hydrophobic plasticizer per weight of the total dosage form.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 02/00890

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/50 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2003	20/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]rmation on patent family members

Internal Application No
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